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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,106	07/10/2001	Henrik Garoff	0825-0166P	8395

2292 7590 02/24/2005

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,106	GAROFF ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,45,51,52 and 63-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,45,51,52 and 63-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP 602.01 and 602.02.

The oath or declaration is defective for the reasons of record in the previous Office Actions (Mailed 4/1/03 and 1/2/04). Applicants have responded to this requirement by indicating that they will submit a supplemental Declaration when the claims are otherwise in condition for allowance. Applicants also indicate that they do not concede that the presently claimed subject matter is not adequately disclosed in the parent PCT application PCT/SE91/00855. The requirement for a new Declaration is therefore maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 43, 45, 51-52, 63-71 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al.

This rejection is maintained for reasons of record in the previous Office Action (Mailed 1/2/04) and for reasons outlined below.

Applicants traverse this rejection by providing arguments and one of the inventors, Dr. Liljestrom, has submitted a Declaration under 37 CFR 1.132. Applicants argue that the specification supports the term "helper cell" because the specification need not use the exact terms recited in the claim in order to show that applicants were in possession of the claimed invention. Applicants also assert that the examiner has clearly understood that the "producer cell" is one in which functions absent from the vector are complemented by the helper RNA so as to produce recombinant alphaviral particles and that the if the examiner asserts that the helper cell is permanently transformed with the complementing nucleic acid, applicants assert that the specification also supports this.

In response, the examiner, after further consideration, concludes that the claimed "helper cells" for producing infectious alphaviral particles are the same as the "producer cells" recited in the specification. However, since the specification does not provide antecedent basis for the claimed term, said specification must be amended to provide support for the claimed "helper cells".

Applicants assert that support for mutations in the E1, E2 or E3 is provided by the specification at page 10, lines 17-20 where the specification allegedly teaches introducing a conditionally lethal mutation into the structural part of the genome (i.e. the capsid or one of the spike proteins (E1, E2, E3). Applicants also point to pages 33 and 34 and Examples 4 and 5 in the specification to show the generation of a conditionally lethal mutation in the E3 part of the p62 protein (which is subsequently cleaved into E2 and E3 during viral infection) and an insertion of a short oligonucleotide into the E2

protein. Applicants submit that the specification thus describes "mutation" of the E1, E2 or E3 proteins.

Applicant's arguments filed 2/1/05 have been fully considered but they are not persuasive. First, applicants' arguments do not address where in the specification support can be found for "at least one mutation" in the E1 protein. With regard to the mutation in the p62 protein which applicants indicate is cleaved into the E2 and E3 proteins, it is noted that the mutation recited by applicants' results in a **noncleavable form of the p62 protein**. Therefore, no E2 and E3 protein is produced and while it can be asserted that the specification provides support for a specific conditionally lethal mutation in the p62 protein, it cannot be asserted that this part of the specification supports at least one mutation in the E3 protein. With regard to the mutation in E2, it is noted that this specific single mutation is an introduction of a unique restriction site to allow insertion of a sequence encoding a foreign epitope in the E2 portion of the SFV genome. The specification does not provide support for "at least one mutation" in the gene encoding the E2 protein, i.e. no support can be found for more than one mutation in the E2 gene. Indeed, the specification does not provide support for more than one mutation in the E2 or E3 genes.

With regard to Claim 65, applicants assert that the examiner has mischaracterized the claim in that the examiner indicated that one of the helper vectors encodes the E1 and E3 proteins rather than the E1 and E2 proteins. Applicants again reiterate their position that the description of Fig. 4 supports their (E1 and E2) inclusion together in a helper vector or in a helper cell.

In response, the examiner notes that applicants are correct in that the claim recites that one of the helper RNAs contains the E1 and E2. The examiner apologizes for the typographical error. However, this does not affect the grounds of the rejection of claim 65. Figure 4 does not in any fashion teach the limitations of claim 65. Figure 4 does not teach a helper cell comprising two helper RNAs wherein the first RNA encodes the E1 and E2 glycoproteins and wherein the second helper RNA encodes the alphavirus capsid protein. Figure 4 shows a **single** vector containing the sequences encoding the E1, E2 and alphavirus capsid proteins.

The Declaration under 37 CFR 1.132 filed 2/1/05 is insufficient to overcome the rejection of claims 43, 45, 51, 52 and 63-71 based upon 35 USC 112, 1st paragraph as set forth in the last Office action because of the following reasons:

Initially, it is noted that the Declaration represents an opinion Declaration concerning the ultimate legal conclusion at issue, that is whether the application complies with 35 USC 112, 1st paragraph (written description). The weight given to such as Declaration is outlined in MPEP 716.01(c):

> Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. *In re Chilowsky*, 306 F.2d 908,134 USPQ 515 (CCPA 1962) (expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight); *In re Lindell*, 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." 385 F.2d at 456, 155 USPQ at 524 (emphasis in original)). In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or

absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986).

With respect to the helper functions being on more than one helper construct, Declarant indicates that assembly of the vector pSP6-SFV4 using "independent overlapping subclones" (Declarant refers to Figs. 2 and 4A-B and p. 29 of the specification) would "suggest" to the skilled artisan together with Figure 2 that the capsid and E1, E2 and 6k proteins can be made on separable transcripts. Declarant also asserts (on p. 4 of the Declaration) that:

> Furthermore, these proteins are made in a non-overlapping sequence and so it would have been understood by the molecular biologist of ordinary skill at the time the application was filed that the structural gene for each of these proteins could be placed under a separate transcriptional promoter and be individually expressed. This is supported by results from our laboratory published prior the priority date the present application which definitely show that one can divide the structural gene region of an alphavirus and express the proteins separately.

Declarant then cites references from their laboratory. Additionally, Declarant recites that the p62 and E1 proteins can be expressed from separate coding units of engineered cDNA sequences and yet can be properly associated in the cell membrane. Furthermore, Declarant asserts that at the time the invention was made, those of skill in the art would have recognized that dividing the helper functions on multiple vectors would help reduce the likelihood of formation of undesirable replication competent vectors during the packaging process. Declarant then cites prior art publications to support the arguments.

In response, the examiner notes that the MPEP recites that newly added claim limitations must be supported in the specification through "**express, implicit, or inherent disclosure**" (See MPEP 2163). In the instant case, the claimed limitations are not supported by express disclosure or by inherent disclosure, i.e. disclosure of all the helper functions being present on a single nucleic acid molecule does not provide express or inherent disclosure of multiple helper RNA molecules. With regard to implicit disclosure, Declarant argues that the instant disclosure would have suggested to the skilled artisan that the helper functions could be divided into different RNA molecules. This represents Declarant's opinion. To bolster said opinion, Declarant refers to publications from the inventors' laboratory or the general scientific literature. This evidence does not provide support for implicit disclosure of the claimed limitations, but instead the cited prior art only may suggest that the skilled artisan may have been motivated to **significantly modify the disclosure**, in a manner not taught or suggested by the instant disclosure, so as to generate the claimed subject matter. This is not sufficient evidence to indicate that the originally filed disclosure provided implicit support for the claimed invention.

Declarant also argues that the specification provides support for at least two kinds of mutations in the spike proteins E2 and E3.

In response, it is noted that the examiner has addressed this issue previously in this Office Action (see above).

Finally, Declarant argues that the specification provides support for the claimed "helper cells". In response, the examiner agrees and this aspect of the rejection is withdrawn.

For the reasons outlined above, the rejection is maintained.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not provide support for the term "helper cells" and must be amended to provide support for the said term.

No Claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
February 22, 2005

DAVID GUZO
PRIMARY EXAMINER